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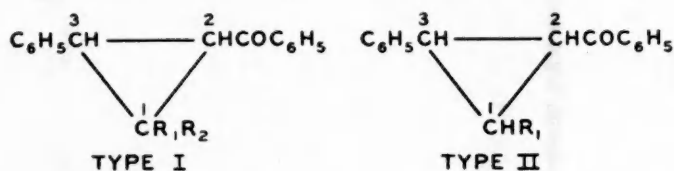
No. 3

The Synthesis and Relative Stability of Certain Ketonic Cyclopropanes

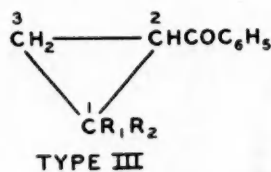
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NUMEROUS investigations of cyclic nonbenzenoid hydrocarbons, prompted largely by Baeyer's strain theory, have revealed that the relative stability of these cyclic structures varies not only with the number of methylene groups in the ring, but also with the kind, number, and arrangement of the substituent groups. Kohler and his students have studied in great detail a large number of highly substituted ketonic cyclopropanes, including the esters and acids represented as Type I and Type II, in which R_1 and R_2 indicate $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$, or $-\text{COOH}$.

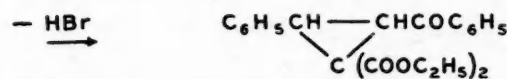
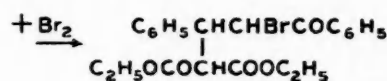
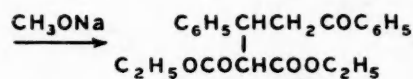
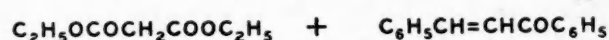


Recently, Allen and Cressman prepared the closely related ketonic derivatives, indicated as Type III, which differ in structure from Type I only in the absence of the phenyl group on carbon atom 3.



The ketonic cyclopropanes studied by Kohler and Conant are prepared with

good yields by adding malonic ester to benzalacetophenone in the presence of sodium methylate. The ketonic ester obtained is readily brominated, forming mainly a γ -bromoester, which easily loses hydrogen bromide on treatment with alcoholic potassium acetate, resulting in closure of the ring.



Frequently, however, this procedure gives a mixture of oily stereoisomeric trimethylenes. This is easily prevented by transforming the monobromoester into the dibromoester and removing bromine from the latter by either zinc dust or alcoholic potassium iodide. The removal of bromine by alcoholic potassium iodide takes place in the cold, indicating the ease of ring formation.

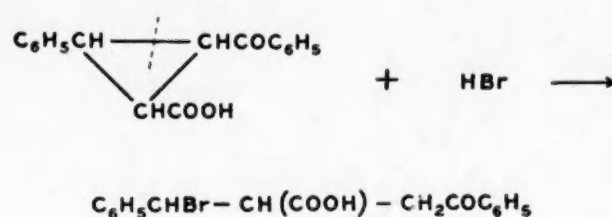
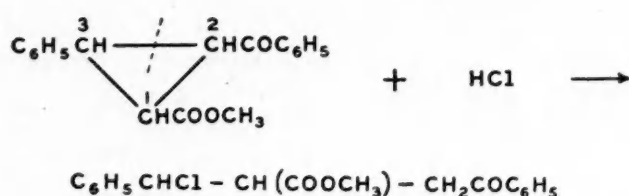
By means of a similar series of reactions, the cyclopropane ester III is ob-

tained from vinyl phenyl ketone. This latter is formed by the action of alcoholic potassium acetate on the more readily available β -chloropropiophenone, resulting in the removal of hydrogen chloride.

Derivatives of II are more difficult to prepare. Small quantities of the acids are always obtained on pyrolysis of the dibasic acids I and III, but the major products are substances resulting from ring cleavage. Kohler and Steele, using an adaptation of Buchner's pyrazoline method for synthesizing cyclopropane carboxylic acids, finally obtained the cyclopropane ester II with 40 per cent yield by heating ethyl 4-phenyl-5-benzoylpyrazoline carboxylate in the presence of polished nickel.

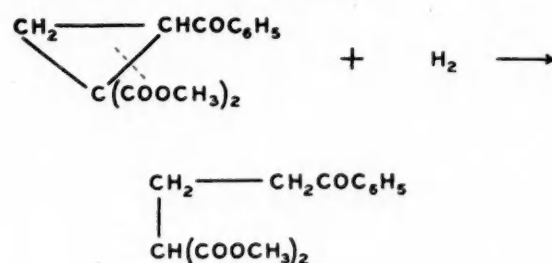
The phenylated ketonic derivatives I are in general much more reactive than the derivatives II and III. The cyclopropane ring in the former has been opened in all three positions, the same reagent often giving two types of product. The ester I is extremely sensitive to dry basic reagents. Alcoholates, ammonia, and amines rapidly and smoothly transform it into an isomeric unsaturated compound, methyl β -benzoyl- γ -phenylvinyl malonate, which could only be formed by ring scission between carbon atoms 1 and 3. The esters II and III are not attacked by dry bases, but in the presence of water, they, as well as the ester I, are hydrolyzed with unusual rapidity by bases to the corresponding cyclopropane carboxylic acids.

The ester and acid II in glacial acetic acid solution are more reactive with halogen acids than either I or III. The ring is opened in the 2:3 position as indicated in the following equations:



Hydrogen bromide in glacial acetic acid solution ruptures the cyclopropane ring of derivatives of I between carbon atoms 1 and 3, and 2 and 3, but the reaction is complicated by secondary reactions that lead to loss of carbon dioxide and lactone formation. Under ordinary conditions, halogen acids in acetic acid solution have no effect on the ester III, but when the reaction is carried out by heating in a sealed tube, cleavage of the ring occurs in the 1:2 position. The same reagent at room temperature slowly transforms the acid III into an open chain bromoacid which loses carbon dioxide on standing, to form a carboxylactone. The latter on pyrolysis loses further carbon dioxide, yielding a γ -benzoylbutyrolactone that could only have been formed by 1:2 opening of the ring. Halogen acids in alcohol solution catalyze re-esterification of the acids I, II, and III to the corresponding esters.

All the cyclic structures represented by I, II, and III are easily reduced by zinc and acetic acid to the corresponding open chain substances; the ring breaks down in each case between the carbon atoms 1 and 2. For example, methyl 2-benzoylcyclopropane-1,1-dicarboxylate (III) is reduced to methyl γ -benzoylethylmalonate in accordance with the equation below:



The cyclopropane esters I, II, and III are stable to heat. They distill under

reduced pressure without decomposition, a fact which in the earlier investigations was the main criterion of stability. The dibasic acid I on pyrolysis yields two stereoisomeric cyclopropane monobasic acids of Type II, two unsaturated acids, a saturated lactone, and two isomeric unsaturated croto-lactones—products that can only be accounted for by 1 : 3 and 2 : 3 opening of the ring. The dibasic acid III on heating forms small quantities of cyclopropane monobasic acids and γ -benzoyl-butyrolactone. The monobasic acid II is stable to heat.

The cyclopropane derivatives I, II, and III, while readily attacked by reagents to which α - β unsaturated ketones are peculiarly sensitive, do not react with ozone, potassium permanganate, and bromine—reagents that attack ethylenic compounds at the linkage between carbon atoms. Kohler and Conant conclude from their study of derivatives I that a cyclopropane ring in which all carbon atoms are nominally saturated, and which con-

tains a carbonyl group in proper position, can form a conjugated system which is identical in properties with α - β unsaturated ketones. This conclusion was substantiated by Carr and Burr in their study of absorption spectra. They conclude that the cyclopropane ring is a center of "residual affinity" similar in character but intermediate in quantity to that of a double bond.

The cyclopropane derivatives III, bearing substituent groups on only two carbon atoms of the ring, are more stable than the phenylated ketones I and II. In all reactions involving the ring, derivatives of Type III are always cleaved between carbon atoms 1 and 2. Derivatives of I break down, depending on conditions and type of reaction, in all three positions. This is definite proof of the existence of a ring compound. The derivatives of II break down either in the 1 : 2 or 2 : 3 position. The mode of addition in all cases, however, is the same; i.e., addition takes place at the ends of the conjugated system.

Eastman Organic Chemicals as Analytical Reagents

XLII REAGENTS FOR POTASSIUM

NITROSO-R SALT

Sideris, *IND. ENG. CHEM. ANAL. ED.*, 9, 145 (1937)

The potassium is precipitated as the cobalti-nitrate and dissolved in sulfuric acid. The cobalt in this solution is determined by adding nitroso-R salt in the presence of sodium acetate. The red coloration which appears is very stable and is compared with standards.

DIPICRYLAMINE

Winkel and Maas, *ANGEW. CHEM.*, 49, 827 (1936)

Potassium forms with dipicrylamine a very slightly soluble salt, suitable for gravimetric determinations, or, by solu-

tion in acetone, for colorimetric determinations. The dipicrylamine is converted by magnesium carbonate to a soluble salt which is added to a neutral or slightly alkaline solution of potassium. The resulting precipitate is washed, dried, and weighed, or dissolved in acetone, and the color compared to standards.

dl-TARTARIC ACID

Szebelledy and Jonas, *Z. ANAL. CHEM.*, 107, 114 (1936)

The potassium is precipitated as the insoluble potassium acid tartrate by means of an alcoholic solution of *dl*-tartaric acid. The precipitate is dissolved and titrated with standard alkali.

The Use of 1,4-Dioxane in Microscopic Technic

FOR THE preparation of thin sections of animal or plant tissue for microscopic examination, the tissues are frequently infiltrated with a substance, such as paraffin, which is easily cut and yet sufficiently rigid to maintain its shape. Before this can be done, it is necessary that the water in the tissues be replaced by a liquid which is miscible with the wax. For preservation of the tissue structure without shrinkage or swelling, it is essential that the removal of the water and the introduction of the replacing liquid occur at practically identical rates. It is further desirable that the liquid used have mutual solubility for both the paraffin wax and water, so the operation can be carried out simply.

The use of 1,4-dioxane in such microscopic technic has been the subject of many articles in recent years. Descriptions of the properties of this liquid and recommendations for its use are given by Graupner and Weissberger, *Zool. Anz.*, 96, 204 (1931) and 102, 39 (1933); Weissberger, Young, and Carleton, *LANCET*, 1279 (1934); Johansen, *SCIENCE*, 82, 253 (1935); Baird, *STAIN TECH.*, 11, 13 (1936); McWhorter and Weier, *STAIN TECH.*, 11, 107 (1936).

The value of the 1,4-dioxane technic is indicated by its adoption in a great number of European laboratories for routine and research, and its increasing application in this country. In view of the special requirements for this work, the laboratories of the Eastman Kodak Company have prepared a grade of 1,4-dioxane which is less expensive than the highly purified material used for chemical reactions.

This new grade, listed in *Eastman Organic Chemicals, List No. 28*, as No. 2144-X, 1,4-Dioxane (Histological), is an anhydrous and peroxide-free product. It is a clear, colorless fluid,

boiling at 101° C. and freezing at 11.7° C., and mixes readily with water, alcohol, and molten paraffin wax. Its molecular weight (88) is considerably higher than that of monomolecular water (18). This does not imply, however, that its rate of diffusion into the tissues is unfavorable compared with the rate at which the water diffuses out of the membranes, since water is a polymer of a rather branched and spacious structure, whereas 1,4-dioxane is not associated, and its molecule—due to the ring structure—is rather compact.

A further advantage of the use of 1,4-dioxane is the fact that after it has absorbed water from the tissues, it can be readily dried by agents such as calcium chloride. The procedure as described by Weissberger, Young, and Carleton is as follows: The tissues, having been fixed, are transferred from the fixative direct to the 1,4-dioxane, which is contained in a small jar on the bottom of which a few granules of calcium chloride or sodium sulfate have been placed. A piece of surgical or zinc gauze can be used to separate the tissue from the dehydrating agent. The duration of treatment in 1,4-dioxane naturally varies with both the thickness and consistency of the tissues. Small, thin pieces become water-free in from 2 to 3 hours, while those of large surface area, but not thicker than 2 to 3 mm., usually are ready for imbedding after treatment overnight (about 12 to 15 hours). The first step in the transfer to paraffin wax is made by placing the tissues in a mixture of equal parts 1,4-dioxane and wax, the whole being kept warm in an imbedding oven for one-half to one hour.

McWhorter and Weier pointed out that in the mounting of sections in balsam, the employment of 1,4-dioxane as a solvent is preferable to xylene.